Pharmacological management of antifungal agents in pulmonary aspergillosis: an updated review.

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Introduction

Aspergillus may cause different types of lung infections: invasive, chronic pulmonary or allergic bronchopulmonary aspergillosis. Pharmacological management with antifungals poses as a challenge. Patients diagnosed with pulmonary aspergillosis are complex, as well as the problems associated with antifungal agents.

Areas covered

This article reviews the pharmacology of antifungal agents in development and currently used to treat pulmonary aspergillosis, including the mechanisms of action, pharmacokinetics, pharmacodynamics, dosing, therapeutic drug monitoring and safety. Recommendations to manage situations that arise in daily clinical practice are provided. A literature search of PubMed was conducted on November 15th, 2020 and updated on March 30th, 2021.

Expert opinion

Recent and relevant developments in the treatment of pulmonary aspergillosis have taken place. Novel antifungals with new mechanisms of action that extend antifungal spectrum and improve pharmacokinetic-related aspects, drug-drug interactions and safety are under current study. For those antifungals already marketed, new data related to pharmacokinetics, pharmacodynamics, dose adjustments in special situations, therapeutic drug monitoring and safety are available. To maximize efficacy and reduce the risk of associated toxicities, it is essential to choose the most appropriate antifungal; optimize its dose, interval, route of administration and length of treatment; and prevent side effects.

Keywords: Allergic bronchopulmonary aspergillosis, antifungals, *Aspergillus*, chronic pulmonary aspergillosis, invasive aspergillosis, isavuconazole, liposomal amphotericin B, pharmacology, posaconazole, voriconazole.

Article highlights

- Patients with different forms of pulmonary aspergillosis present with special characteristics (advanced age, immunosuppression, organ impairment, hypoalbuminemia, underweight/obesity, polypharmacy, drug-drug interactions or intolerance).

- Available antifungal agents pose several limitations, rendering pharmacological management a challenge.

- Novel antifungals are under development. These drugs provide new mechanisms of action, broaden the spectrum, including azole-resistant strains and cryptic species, and improve pharmacokinetic-related aspects, drug-drug interaction profiles and safety of available agents.

- Data on the pharmacokinetics (including drug-drug interactions), pharmacodynamics, dosing, therapeutic drug monitoring and safety are up to date on current agents available, including management recommendations for situations that arise in daily clinical practice.

1. Introduction

Aspergillus is a ubiquitous, soil-dwelling fungi that may cause a wide range of pulmonary diseases: invasive aspergillosis (IA); chronic pulmonary aspergillosis (CPA): subacute invasive aspergillosis, aspergilloma, chronic cavitary pulmonary aspergillosis (CCPA), chronic fibrotic pulmonary aspergillosis (CFPA); as well as allergic forms such as allergic bronchopulmonary aspergillosis (ABPA) or severe asthma fungal sensitization [1–3]. The most relevant species are *A. fumigatus, A. flavus, A. niger, A. terreus* and *A. nidulans* [1,4]. However, cryptic species have also grown in importance in recent years, often showing resistance to triazoles and polyenes [5,6].

IA normally affects immunosuppressed patients such as either those with hematologic disorders, solid organ transplantations, cirrhosis or chronic pulmonary obstructive disease (COPD), or those critically ill [2,3]. Furthermore, patients with viral pneumonia, i.e. due to influenza or COVID-19, face an increased risk of pulmonary aspergillosis [7]. CPA affects patients with or without little immunosuppression yet with pre-existing lung disease as active or previous mycobacterial infection or COPD [3,8]. Allergic forms occur mainly in patients with asthma or cystic fibrosis as a result of a hypersensitive reaction to *Aspergillus* [3,9,10]. Overall, patients diagnosed with various forms of pulmonary aspergillosis will present with different characteristics such as advanced age, immunosuppression, organ impairment, hypoalbuminemia, underweight or obesity, polypharmacy, drug-drug interactions (DDI) or intolerance. Such variables influence the pharmacology of the drugs [10–13].

Current antifungal armamentarium includes three drug classes: triazoles, polyenes and echinocandins. There are several limitations, including reduced bioavailability, lack of oral administration, variable pharmacokinetics (PK), need for therapeutic drug monitoring (TDM), DDI, drug toxicities and high costs [1].

As a result of both patient characteristics and drawbacks posed by the drugs, pharmacological management with antifungal agents becomes a real challenge for clinicians.

At the same time, it is worth mentioning that while previous studies have already reviewed the pharmacology of antifungals used in aspergillosis treatments [8,14–16], new studies have come to light. Compounding these scientific discoveries are novel molecules like isavuconazole, super-bioavailable (SBA)-itraconazole or posaconazole delayed-release tablets that recently received approval and breakthrough drugs with new targets (rezafungin, ibrexafungerp, olorofim or fosmanogepix) currently under investigation [1,17].

For these observations, advanced knowledge and optimization of pharmacological therapy will become even more essential if treatment outcomes of patients are to improve.

The aim of this work is to review the pharmacology of antifungal agents indicated to treat the different forms of pulmonary aspergillosis. We include management recommendations of situations that arise in daily clinical

practice. However, as this paper focuses on pulmonary aspergillosis, these recommendations may vary in cases of extrapulmonary aspergillosis.

2. Data sources

We conducted a literature search in PubMed and Clinical Trials registry (www.clinicaltrials.gov) on November 15th, 2020 and updated it once more on March 30th, 2021. We described the literature search method in the Supplementary Material. We limited results to articles written in English only.

3. Clinical use

Triazoles remain the cornerstone of treatment, with liposomal amphotericin B (L-AmB) and echinocandins serving as alternatives [1,18]. We summarize the clinical use of antifungal agents among the different forms of pulmonary aspergillosis in Table 1.

4. Pharmacology of antifungals

4.1 Mechanisms of action and resistance

We describe the mechanisms of action in Figure 1 and mechanisms of resistance in the Supplementary Material.

4.1.1 Triazoles

Triazoles act by inhibiting cytochrome P450 (CYP450, notably CYP51A) enzyme lanosterol-14-alpha-demethylase [19]. This inhibition leads to the termination of ergosterol synthesis, resulting in a depletion of ergosterol, disruption of the cell membrane and thereby cessation of fungal growth [19–21]. Accumulation of methylated intermediates also generates direct fungal cell toxicity [20,21].

4.1.2 Polyenes (L-AmB)

Polyenes bind to ergosterol, creating pores or ion channels that lead to ion leakage (K^+, Mg^{++} and other organic substrates) and cell death thereafter [18,22,23]. Other mechanisms include the inhibition of fungal proton-ATPase; auto-oxidation of polyenes that produce superoxide, hydrogen peroxide and hydroxyl radicals that oxidize lipid membranes; or formation of extramembranous aggregates that extract ergosterol from lipid layers [18,23,24]. Furthermore, polyenes may modulate macrophage activity [25].

Different preparations of amphotericin B (AmB) exist, including deoxycholate (d-AmB), lipid complex and L-AmB. These have already been compared and are briefly discussed in the Supplementary Material [23,25,26].

4.1.3 Echinocandins, including rezafungin and ibrexafungerp

Echinocandins non-competitively inhibit the FKS subunit of the β-(1,3)-D-glucan synthase, blocking the synthesis of β-(1,3)-D-glucan, an important component of the cell wall [27–29]. This disruption leads to a leaky and highly permeable cell wall, and an imbalance in the intracellular osmotic pressure occurs [27]. Additionally, echinocandins decrease tissue invasion by damaging the hyphal tips and branch points of growing cells and resulting in the irregular growth of hyphae with branched tips and distended cells [29]. Echinocandins may also show immunomodulatory effects [30]. Rezafungin is a novel drug that derives from anidulafungin, whereas ibrexafungerp is a novel, first-in-class oral triterpenoid inhibitor [17,31]. Ibrexafungerp acts by inhibiting the FKS subunit as well. However, this particular drug binds to another part of the enzyme [17,31].

4.1.4 Olorofim

Olorofim belongs to a new class of antifungals called the orotomides [17]. Olorofim inhibits dihydroorotate dehydrogenase (DHODH), a central enzyme involved in pyrimidine biosynthesis [17]. This process prevents the formation of uridine-5'-triphosphate (UTP), which is required for the production of UDP-sugars. As these sugars are substrates for β-(1,3)-D-glucan synthase and chitin synthase, olorofim blocks cell wall synthesis [32]. The inhibition of UTP formation may also lead to decreased production of DNA/RNA pyrimidine derivatives like cytosine, thymine or uracil, which are essential in developing precursors related to lipid and carbohydrate metabolism and DNA synthesis [1,32].

4.1.5 Fosmanogepix

Fosmanogepix is a prodrug that, once converted to manogepix, inhibits the enzyme *Gwt1* [17,33]. *Gwt1* catalyzes the inositol acylation of fungus-specific glycosylphosphatidylinositol (GPI)[1]. Its inhibition leads to the disruption of GPI-anchored protein (mannoproteins) maturation, weakening the cell wall [1]. GPI cell wall anchor proteins also play a role in enzymatic activity, signaling, cell adhesion, cell wall metabolism and immune response [1]. The GPI-anchored proteins are covalently linked to β-(1,3)-D-glucan, which help maintain fungal cell integrity [17]. When GPI-anchor synthesis is disrupted, β-(1,3)-D-glucan becomes more exposed, and recognition of the polysaccharide by immune cells increases [17].

4.2 Pharmacokinetics

The PK of different antifungals comprise a fundamental aspect when considering the most appropriate treatment to select [15]. The most relevant pharmacokinetic-related aspects are gathered in Table 2.

Of the approved drugs, only triazoles are available via the oral/enteral route; these drugs have a varying range of bioavailability. Acid-suppressive medications such as proton pump inhibitors (PPI) or antihistamine agents reduce the absorption of some triazoles. For this reason, it may be worth reassessing the need of such medications, especially as clinicians often yet unnecessarily prescribe them [34]. If not possible, switching to another triazole formulation may be necessary [35–37]. With the introduction of novel drugs like

isavuconazole and breakthrough formulations such as SBA-itraconazole or posaconazole delayed-release tablets, these problems have decreased in frequency [19,35,37]. Other upcoming drugs with oral formulations include ibrexafungerp, olorofim and fosmanogepix [17].

Most of the antifungals are lipophilic, which may explain their great volume of distribution. Due to this lipophilicity, some formulations (itraconazole oral solution, intravenous itraconazole, voriconazole, posaconazole and olorofim) require a sulphobutylether-β-cyclodextrin to increase solubility [21,36–38]. Excluding voriconazole, antifungals highly bind to plasma proteins, mainly albumin [14].

Drug penetration into affected tissue serves as another important, differentiating factor among the different forms of pulmonary aspergillosis. In early-stage IA, penetration into epithelial lining fluid (ELF), alveolar epithelial cells and pulmonary alveolar macrophages would be pertinent [39]. In cases where an established disease is diagnosed, the relevant tissue lie within the nodule and pulmonary parenchyma. Finally, pulmonary parenchyma grows in relevance during late-stage disease: there is the additional challenge of administering drug concentrations that are therapeutic in a relatively avascular area.

In subacute IA, chronic cavitary pulmonary aspergillosis and chronic fibrotic pulmonary aspergillosis, pathophysiological changes affect antifungal penetration and thereby impact clinical outcomes and treatment duration [40]. In subacute IA, infection develops in parenchymal lung tissue. This fact may explain better outcomes observed with reduced treatment duration when compared to chronic cavitary forms [40]. In CCPA and CFPA, a cavity surrounded by fibrotic tissue develops, rendering antifungal penetration difficult and prompting prolonged treatment duration [40].

Most antifungals are eliminated through liver metabolism, mainly via CYP450, with minimal urine excretion. This leads to one of their biggest problems, especially in relation to triazoles: drug-drug interactions. In the United States (US), 86-93% of patients receiving a triazole experienced a DDI, although 20-68% were contraindicated [41]. A careful check is therefore advised before and at the end of any treatment with any of the antifungal agents. A summary on the management of potential DDI is provided in the Supplementary Material.

4.2.1 Triazoles

4.2.1.1 Itraconazole

Itraconazole presents non-linear PK, with highly variable plasma levels [38]. Erratic absorption of itraconazole is one reason for this occurrence, although the solution form does improve it. Unfortunately, the solution presents a higher incidence of gastrointestinal side effects, perhaps due to cyclodextrin [18]. A new formulation (SBA-itraconazole) with a higher bioavailability and reduced variability has received approval in the US [35,42].

This triazole is highly lipophilic, facilitating extensive penetration into lung tissue, including the walls of the cavity or fungal balls [14,24,39,43,44]. Itraconazole is metabolized via CYP3A4, with hydroxy-itraconazole being produced [14,38]. Its concentration is approximately twice that of itraconazole, exhibiting a comparable, potent and strain-dependent antifungal activity [38,45]. These metabolites are mainly excreted in the bile, with 3-18% of non-absorbed itraconazole excreted unchanged in feces [38].

Itraconazole is a potent inhibitor and substrate of CYP3A4 and P-glycoprotein [14,46]. Caution is advised when initiating triazoles (especially itraconazole) in allergic bronchopulmonary aspergillosis, as interactions with oral and inhaled corticosteroids may occur.

4.2.1.2 Voriconazole

Voriconazole is a second-generation, fluconazole-derived triazole [21]. Voriconazole presents non-linear pharmacokinetics with high interindividual variability in plasma levels [21,47]. It allows for rapid absorption (<1.7 hours), providing a fast switch to the oral route [21]. The drug is widely distributed in tissue, including the ELF [21,44,48].

This drug undergoes extensive metabolism via hepatic CYP2C19 (the major route), CYP2C9 and CYP3A4 [21]. The genetic polymorphism of CYP2C19 significantly influences metabolism of the drug [21]. Standard dose would only be appropriate for normal metabolizers, while an estimated dose increase by 100% and 300% would be necessary for rapid and ultra-rapid metabolizers, respectively [49]. A dose reduction by 50-75% would otherwise be obligatory for intermediate and poor metabolizers. Therefore, clinicians should prescribe voriconazole on an individualized basis in accordance with CYP2C19 and TDM [49].

Saturation of the drug's metabolism is also responsible for the non-linear PK [21]. Severe inflammation may affect metabolism of voriconazole, since increments in C-reactive protein (CRP) may downregulate CYP2C19 (an increase of 0.015 mg/L in trough values was determined for every CRP increase of 1 mg/L)[24,44,50]. Metabolites (without antifungal activity) are mainly eliminated in the urine (80%) and bile (20%)[21].

4.2.1.3 Isavuconazole

Isavuconazole is administered as the prodrug isavuconazonium sulfate, with isavuconazole being the active moiety obtained after rapid hydrolysis by plasma esterases [19,20]. Exposure to isavuconazonium is negligible [19,20].

An advantage of this drug is its low-to-moderate interindividual variability, with low intra-patient variability and linear PK [19,51–53].

Oral and intravenous forms may be used interchangeably [19,20]. Isavuconazole presents a wide volume of distribution, including significant lung penetration [44,48]. Metabolism of the drug occurs via CYP3A4/3A5, with inactive metabolites being eliminated through feces (46.1%) and urine (45.5%)[19,20].

Furthermore, lower inhibition of CYP3A4 gives isavuconazole an advantage when compared to triazoles, as a better interaction profile is possible [20]. This is of special interest in patients treated with immunosuppressive drugs like tacrolimus, sirolimus or cyclosporine; isavuconazole provides the best DDI profile [20].

4.2.1.4 Posaconazole

Posaconazole is derived from itraconazole, showing a similar chemical structure yet being less lipophilic [37,48]. Posaconazole suspension presents erratic and satiable absorption: however, delayed-release tablets have resulted in improvements [37,54]. A novel intravenous formulation has also been recently developed. Both formulations offer less interindividual variability and higher and more consistent plasma concentrations [37,46,55]. Unlike solution, tablets exhibit linear PK [37,56]. Posaconazole accumulates in lung tissue, especially in macrophages [37]. This characteristic allows for the long duration of action commonly observed in epithelial cells [57].

This triazole is mainly metabolized by hepatic uridine glucuronosyltransferase (UGT) 1A4, without significant oxidation by CYP450 [58]. It is a substrate of P-glycoprotein and a potent inhibitor of CYP3A4, which is concentration-based and therefore formulation-dependent [36,37]. Approximately 77.0% of the dose is excreted in feces [24,37,58].

Given available evidence, the linear PK and modest elimination via CYP3A4, posaconazole may be the preferred triazole when, under strict TDM, co-administration of triazoles and rifamycins is necessary [56]. Although rifampin may induce P-glycoprotein and UGT, there is a paucity of data regarding its impact on serum levels [56,58]. Previous reports have demonstrated sub-therapeutic concentrations with posaconazole solution and rifamycins [56]. Delayed-release tablets may solve this problem. Two case reports showed that a posaconazole dose of 300 mg every 12h (q12h) achieved therapeutic levels when co-administered with rifampin [56].

4.2.2 L-AmB

L-AmB presents linear pharmacokinetics at dosages employed for aspergillosis (3 mg/kg/q24h), with nonlinearity present at higher dosages (7.5-15 mg/kg/q24h)[59]. This drug exhibits a high volume of distribution [22,60]. Inflammation and infection may increase pulmonary concentrations, as threefold-higher levels were detected in infected areas when compared to those non-infected [25,26,39,61].

This polyene mainly binds to albumin and α-1-acid-glycoprotein, leading to the existence of simultaneous plasma liposomal binding, protein binding and unbound L-AmB [62]. Bound plasma concentrations increase with L-AmB concentration [62]. As a result of sequestration by circulating liposomes, L-AmB elevates total drug concentration while reducing unbound concentration [62].

Urinary and biliary elimination as an unchanged drug has been proposed, although the exact mechanisms are unknown [22]. Renal and fecal clearance probably occur after liberation from liposomes, thereby explaining the lower urinary (4.5% vs. 20.6%) and fecal (4.0% vs. 42.5%) concentrations when compared to those of D-AmB [62]. These properties may also give reasoning as to its safer profile when compared to other polyenes [62]. L-AmB is not related to drug-drug interactions.

Concerning lung penetration of nebulized L-AmB, it achieves adequate concentrations in the ELF (3.0-11.1 mg/L)[63].

4.2.3 Echinocandins

Echinocandins are lipophilic drugs with a variable volume of distribution [27]. These drugs are mainly found in the lungs, in macrophages specifically, with poor distribution in tissue and the ELF [39,44].

Anidulafungin is eliminated slowly by chemical degradation into an inactive metabolite in the plasma. Given the lack of hepatic metabolism, DDI are, therefore, unexpected [64]. Caspofungin may also degrade. However, like micafungin, it undergoes hepatic metabolism to form inactive metabolites [27,29,65]. These metabolites are then eliminated by bile in feces [27]. Although these two drugs are poor substrates for P-glycoprotein transporters or CYP450, they may be subject to drug-drug interactions [27].

4.2.4 Rezafungin

Rezafungin penetrates well into the tissue, including the lungs, without significant drug-drug interactions [44,66,67]. Its most notable PK feature is its long half-life (80 hours after the first dose and 150 hours after the second or third doses). Due to this particular property, it allows for an extended, once-a-week administration interval [17]. This half-life also enhances drug penetration into tissue [68]. Rezafungin presents minimal urinary excretion [68].

4.2.5 Ibrexafungerp

Ibrexafungerp is a lipophilic compound with oral formulations, although the use of PPI reduces its bioavailability [31,69]. It presents extensive distribution, including in the ELF and lung tissue [31,70]. It undergoes hepatic metabolism by CYP450 isoenzymes, becoming a substrate of CYP3A4 and modest inhibitor of CYP2C8 [31,70]. Ibrexafungerp is eliminated through bile and feces (90%), as well as urine (1.5%)[31,69,70].

4.2.6 Olorofim

Olorofim may be orally administered. It has wide distribution in the lung and is a weak inhibitor of CYP3A4 [32]. Olorofim may present significant enterohepatic circulation, with negligible urinary elimination [32].

4.2.7 Fosmanogepix

Fosmanogepix is rapidly metabolized by systemic alkaline phosphatases into its active form, manogepix [1,33,71]. It presents a wide volume of distribution and penetrates well into lung tissue. Fosmanogepix is mainly eliminated in bile and feces [71], albeit not via CYP450 [71].

4.3 Pharmacodynamics

Knowledge of the PD index that best describes antifungal activity (Table 2) is of the utmost importance when optimizing antifungal killing [72]. Antifungal activity pattern, including the significance of post-antifungal effects, is detailed in the Supplementary Material.

The antifungal spectrum and activity of different antifungal agents are included in Table 3.

4.3.1 Triazoles

Triazoles exert their fungicidal activity in a concentration- and time-dependent manner [72,73].

4.3.2 L-AmB

L-AmB presents concentration-dependent fungicidal activity [23,61,72,73]. *A. terreus* is resistant to L-AmB, so therapy with triazoles is necessary [55].

4.3.3 Echinocandins

Echinocandins show concentration-dependent fungistatic activity [72,73]. Although activity of the three echinocandins is comparable, anidulafungin may present the highest *in vitro* activity against *Aspergillus* spp. [28].

Caspofungin confers a “paradoxical effect”, which has only been demonstrated *in vitro* [28]. This phenomenon consists of fungi growth within the presence of high concentrations that significantly exceed the minimum inhibitory concentrations (MIC); it is not normally observed with other echinocandins [28]. The potential mechanism is summarized in the Supplementary Material. Although this observation is more common in *A. fumigatus*, it may also arise in *A. flavus*, *A. terreus* or *A. niger* [30]. The clinical effects of this particular event are unknown.

4.3.4 Rezafungin

Unlike caspofungin, no paradoxical effects were observed *in vitro* [74]. Rezafungin exhibits activity similar to other echinocandins, with *in vitro* activity against azole-resistant *A. fumigatus* and other cryptic species with reduced susceptibility to posaconazole or voriconazole [17,74].

4.3.5 Ibrexafungerp

This agent showed potent *in vitro* activity against the main species of *Aspergillus* spp., with lower MIC_{50} (<0.06-0.06 mg/L) than voriconazole or L-AmB [31]. It retains activity against azole- or echinocandin-resistant strains, as well as against cryptic species [17,31,69].

4.3.6 Olorofim

This drug presents fungicidal action against *A. fumigatus* with prolonged exposure [32,75]. It exhibits time-dependent activity [32]. Olorofim showed potent *in vitro* activity against wild-type (MIC_{90} 0.031-0.125 mg/L) and azole-resistant (MIC_{90} 0.031-0.25 mg/L) *A. fumigatus* [5,17,32,76,77]. This orotomide was the only active drug against all cryptic species of *Aspergillus*, showing lower MICs (0.017-0.098 mg/L) than L-AmB, voriconazole or posaconazole [5].

4.3.7 Fosmanogepix

This drug exhibits potent *in vitro* activity against wild-type, azole- and polyene-resistant strains of *Aspergillus* spp. [1,71]. Minimum effective concentrations $(MEC)_{90}$ were 0.015-0.06 mg/L against the four main relevant *Aspergillus* species [71]. Fosmanogepix also showed potent activity against *A. lentulus* and *A.calidoustus* (MEC_{90} 0.03-0.06 mg/L)[1].

4.4 Dosing

Several factors may affect antifungal pharmacokinetics conditioning drug dosing: obesity, cachexia, renal and hepatic impairment, the use of continuous renal replacement therapies (CRRT), extracorporeal membrane oxygenation (ECMO) or hypoalbuminemia. The exact mechanisms of their influence are described in the Supplementary Material. Unfortunately, high quality evidence on dosing adjustments in these populations is lacking [73]. TDM is, therefore, routinely recommended. However, as TDM is not always available, potential dosage adjustments are provided (Table 4). We suggest to carefully individualize dosing based on the severity of the infection, risk of side effects, type of aspergillosis and organism susceptibility.

Clinicians could consider different treatment regimens per the type of pulmonary aspergillosis [54]. For example, patients diagnosed with invasive aspergillosis often present mucositis or diarrhea, which can lead to worse oral absorption [37,38]. However, patients with chronic pulmonary or allergic bronchopulmonary aspergillosis may be able to absorb medication better, so as to reach higher plasma levels. This real possibility combined with prolonged treatment required in these types of diseases increase the risk of side events [54].

A dose reduction may be warranted in this series of patients, especially if elderly, or with low body weight or with previously high levels of other triazoles [54].

4.4.1 Triazoles

4.4.1.1 Itraconazole

No specific adjustments are recommended, except in continuous veno-venous hemodiafiltration [50]. Hypoalbuminemia was associated with a higher incidence of invasive fungal infections, which may be related to lower plasma levels [78]. Close clinical monitoring is advised for these patients and an increase in dose should be considered.

4.4.1.2 Voriconazole

In obese patients, the use of total body weight (TBW) was associated with supratherapeutic levels [79]. The use of ideal or adjusted body weight (ABW) should, therefore, be considered with early TDM [73,80,81]. However, the use of TBW could be initially considered in patients with severe disease—despite the lack of specific clinical data—due to the high variability of plasma levels and risk of underdosage. Thereafter, once the patient has improved, dose could be adjusted based on ABW and/or TDM.

Intravenous voriconazole should be avoided in patients with creatinine clearance <50 mL/min given cyclodextrin accumulation (associated with nephrotoxicity *in vitro*)[21].Clinical relevance of this toxicity is uncertain, though. Several reports have shown its safety, especially if given for a short period [82–84]. A cumulative dose of ≥400 mg/kg may predict worsening renal function [84]. Careful consideration should be taken and oral route preferred, if possible. Another option is switching to isavuconazole, which does not contain this excipient [19,20]. In patients with intermittent hemodialysis or CRRT, cyclodextrin is eliminated [14].

ECMO may extract voriconazole by sequestration, potentially reducing plasma exposure [85]. In these patients, higher initial dosing may be considered together with early TDM [86]. Frequent plasma measurements are advised, as saturation of binding sites on the ECMO circuit may lead to supratherapeutic levels [86].

Dose adjustments in patients with Child Pugh A/B have already been reviewed [21]. In Child Pugh C, a loading dose (LD) of 200 mg q12h followed by a maintenance dose (MD) of 50 mg q12h or 100 mg q24h, with early TDM, were recently recommended [87]. Another PK study recommended different regimens based on total bilirubin levels: 51-171 µmol/L (3-10 mg/dL), LD of 200 mg q12h, MDs of 50 mg q12h or 100 mg q24h; >171 µmol/L (10 mg/dL), same LD, MD of 50 mg q24h [88].

A study conducted in critically ill patients with hypoalbuminemia (<3.5 g/L) showed higher, unbound plasma concentrations, with a more pronounced correlation with increased bilirubin concentrations [89]. The elevated, unbound concentrations could lead to a further risk of side effects, perhaps due to metabolism saturation. A formula was proposed to adjust total measured voriconazole levels in patients with hypoalbuminemia and high bilirubin plasma levels who experience side effects.

4.4.1.3 Isavuconazole

Similar to voriconazole, isavuconazole MD may be reduced in patients with CPA [90]. No other dosage adjustments appear necessary, although new data will become available as use of such drug increases. Regarding ECMO, a case report described circuit sequestration and a drug loss of 17% [91]. Similarly, a separate study showed lower plasma levels in patients with CRRT or ECMO [92]. Standard dosage is recommended with TDM.

4.4.1.4 Posaconazole

Oral solution and tablets are not interchangeable; intravenous dosing, however, may be maintained when switching to oral tablets [37].

Obesity may cause a higher risk of lower plasma concentrations [73,81]. In patients treated with an intravenous formulation, larger LD and MDs based on weight are recommended [93,94]. Although these recommendations may translated into oral formulations, specific evidence is lacking [93].

Hypoalbuminemia could affect dosing of intravenous and tablet posaconazole depending on whether the unbound or bound drug is measured [94–96]. Hypoalbuminemia does not alter dosing requirements when unbound drug is used. However, a dose increase is necessary due to suboptimal levels when total concentrations are measured [94–96]. Therefore, unbound drug concentrations are preferred for these patients, with consideration of a dose increase if TDM is not available [94].

4.4.2 L-AmB

Pre-clinical studies showed that higher doses of L-AmB could improve clinical outcome [22,97,98]. However, the use of 10 mg/kg compared to 3 mg/kg did not improve clinical outcomes or survival rate at 12 weeks in a randomized controlled trial (RCT) [99]. Conversely, the high-dose group presented with a higher rate of side effects (mainly nephrotoxicity and hypokalemia)[99]. Administering a test dose could be considered to reduce the incidence of side effects. For example, clinicians could administer a 1-mg infusion of L-AmB for approximately 10 minutes and observe the patient for 30 minutes thereafter to detect any allergic or anaphylactic reactions [100].

Regarding obese patients, no clear recommendations are present [22,81]. A linear yet small increase of central volume of distribution was found in a recent study, suggesting limited disposition of the drug in adipose tissue. Area under the curve (AUC) and maximum plasma concentration (C_{max}) increase when L-AmB dosing is considered by weight; absolute dose rises, whereas clearance does not change. Therefore, authors propose a weight of 100 kg, e.g., 300 mg if 3 mg/kg, to reduce the risk of toxicity. Other authors recommend the use of ABW for less severe infections, while TBW is more recommendable in severe disease [81]. Like voriconazole, TBW could be used in severe infections during initial days; if clinical improvement occurs, a dose adjustment may be considered.

ECMO may affect L-AmB concentrations. Careful clinical monitoring and consideration of a dose increase are necessary. One case report found L-AmB drug sequestration in the ECMO circuit as a plasma C_{max} of 92.5 mg/L, with pre-and post-oxygenator levels of 91.8 mg/L and 63.3 mg/L, respectively [91].

The potential influence of hypoalbuminemia remains unknown. In a physiologically-based pharmacokinetic model, both L-AmB and released AmB concentrations were reduced when compared to healthy subjects, perhaps due to higher distribution [101]. The clinical implications of this finding are, however, difficult to ascertain. In patients with hypoalbuminemia, a decrease in the L-AmB plasma concentrations may not lead to more elimination. As elimination is mainly due to the liberated AmB, a decrease in the L-AmB plasma concentrations may instead increase distribution into infected tissue [101]. Recommendations for nebulized and percutaneous L-AmB dosing are also described in Table 4.

4.4.3 Echinocandins

In those under CRRT, a higher dose of either caspofungin and micafungin may be considered due to the potential increase in volume of distribution and filter adsorption [102,103].

Data on ECMO remains inconclusive. One study highlighted that ECMO affected caspofungin, whereas another study did not find any significant difference [86,104]. Consequently, a dose increase could be considered in patients diagnosed with either severe disease or an inadequate clinical course. Micafungin plasma concentrations may decrease by up to 23 %, so clinicians should consider an increase in dosage [103,105].

MD of caspofungin could be reduced to 35 mg in patients with Child Pugh B [24]. However, this recommendation may not be applicable in patients admitted to the intensive care unit. In this setting, this reduction may lead to decreased exposure and result in suboptimal clinical outcomes [24]. Neither micafungin nor anidulafungin require dosage adjustments in patients with hepatic impairment [24,64]. Anidulafungin may be preferred in patients with pre-existing liver injury, because it does not undergo hepatic metabolism [64].

Hypoalbuminemia may alter echinocandin pharmacokinetics. However, this observance has only been demonstrated with caspofungin, wherein hypoalbuminemia correlated with low AUC and high clearance [106].

4.5 TDM

The importance of TDM and clinical scenarios for which it is recommended has been reviewed elsewhere and are summarized in the Supplementary Material [45,47].

Most evidence on TDM relates to IA; data on therapeutic goals in chronic or allergic forms are scarce [54,55]. In terms of safety, given the current knowledge of exposure-toxicity relationships, the same goals may be considered. With respect to efficacy—and without forgoing the consideration of patient characteristics (better absorption, prolonged treatment duration, lower fungal burden except in bilateral or severe diseases)—a lower threshold could be contemplated, especially if side effects occur [107,108]. However, given the risk of resistance development and limited evidence, this approach should be considered with caution when side effects arise or other options are not available; strict monitoring would be necessary. TDM recommendations for triazoles are included in Table 5.

4.5.1 Triazoles

4.5.1.1 Itraconazole

TDM of itraconazole is routinely recommended due to variability in plasma levels [47,55]. In chronic pulmonary aspergillosis, subtherapeutic levels (<0.5-1 mg/L) were associated with treatment failure and resistance development [109]. In allergic bronchopulmonary aspergillosis, adequacy of plasma levels (defined as > 2 mg/L) was significantly associated with remission [110]. Based on these studies, and despite the low-quality evidence, a trough level >1-2 mg/L should be warranted.

4.5.1.2 Voriconazole

High interindividual variability in PK of voriconazole requires routine use of TDM [21,55]. Although TDM has been widely recommended to ensure efficacy and safety in forms other than IA, specific goals are lacking [4,8,10,47,55]. In CPA, a trough level of 0.5 mg/L was effective and a safer option [107]. This value was also recommended as the lowest threshold associated with efficacy in a systematic review and meta-analysis [108].

4.5.1.3 Isavuconazole

TDM of isavuconazole is not routinely recommended due to its pharmacokinetic properties and the lack of established concentration-effect and concentration-toxicity values [53,55]. Standard dosages achieved adequate exposures in >90% of simulated patients with MICs ≤1 mg/L in RCT of IA [111]. In routine clinical practice, more than 90% of patients presented a concentration >1 mg/L with standard dosages, which may

therefore not require routine TDM [112]. However, it may still be indicated in some circumstances: lack of response, unexpected toxicity, high MICs, non-compliance suspicion, obesity, cachexia, drug-drug interactions, CRRT/ECMO, hepatic failure or age <18 years [55,91,92,112]. Further studies will determine the role of TDM of isavuconazole.

In patients with CPA, standard dosages yielded a mean level of 4.1 mg/L, with all patients achieving therapeutic levels (>1 mg/L)[90]. A subgroup analysis of the 100 mg q24h dose showed that all patients reached adequate levels with better tolerance than standard doses, suggesting that lower MDs could be considered. A cut-off of 4.6 mg/L best predicted the development of side effects.

4.5.1.4 Posaconazole

Routine TDM is advised with solution [45,47,55]. In contrast, TDM is not usually performed when intravenous and delayed-release formulations are employed, given their PK characteristics [45,55]. Some experts recommend it, regardless, in case of inadequate clinical course, suspected toxicity, hypoalbuminemia, high MIC, obesity/cachexia or critical status [45,50,55].

Although no cut-off for exposure-toxicity exists in IA, an upper plasma toxicity limit of 3.75 mg/L was established during the development of delayed-release tablets [50].

In CPA, 200 mg q24h of posaconazole delayed-release tablets achieved similar plasma levels with a better safety profile than 300 mg q24h [54]. A lower MD could, therefore, be used.

TDM of L-AmB and echinocandins is not routinely recommended [47,61,64].

4.6 Safety

Side effects associated with antifungals are one main drawback. Thus, knowledge and early management of such events are of the utmost importance to improve treatment outcomes [46].

These side effects are well-known and pictured in Figure 2, while mechanisms of such drugs are detailed in the Supplementary Material [23,25,46].

4.6.1 Triazoles

This family of drugs has been widely used for years and therefore presents a well-known safety profile [46]. Besides clinical follow-up, treatment monitoring should include blood pressure, electrolytes, electrocardiography, lipid profile, hepatic biochemistry and, where available, 11β-deoxycortisol—mainly when itraconazole and posaconazole are used [38].

4.6.1.1 Itraconazole

The main side effects of itraconazole are gastrointestinal [38,113]. Like posaconazole, it may cause pseudo-hyperaldosteronism, which may lead to hypertension, hypokalemia, congestive heart failure and peripheral edema [38,46]. A switch to a structurally different azole, i.e., voriconazole or isavuconazole, should be considered in these cases [114].

An increase in liver enzyme levels was described in 17.4% of patients, with 1.5% requiring treatment discontinuation [115]. Cushing syndrome (especially with concomitant corticosteroids) or hair loss are other potential side effects [38].

Most of these effects are reversible upon treatment discontinuation or after lowering dosage [38,116]. When itraconazole allergy is present, a graded voriconazole dose could be considered [117].

4.6.1.2 Voriconazole

This drug may induce transient visual disturbances: abnormal vision, color vision changes (a shift from colors of longer wavelengths as yellow to those of shorter wavelengths as cyan and purple) and/or photophobia [21,46,118]. They are normally reversible even when the drug is continued, not being related to plasma levels [46,47,108].

These symptoms must be distinguished from the neurological toxicity: visual or auditory hallucinations, altered mental status, agitation or involuntary myotonic movements [46,108]. This toxicity was associated with levels >4.0 mg/L [46,108].

Hepatotoxicity is one of voriconazole's main side effects, found in 21.5 % of patients and leading to treatment discontinuation in 14.7 % [115]. This was associated with levels >3 mg/L [47,108]. Isavuconazole or posaconazole may be safe alternatives in case of hepatic toxicity [24,119].

Dermatological reactions are common and can affect up to 42 % of patients [120,121]. They mainly consist of rash and phototoxicity, although other rarer events as toxic epidermal necrolysis and erythema multiforme can also occur [21,120–122]. In patients under long-term treatment, squamous cell carcinomas, melanomas, alopecia (in the scalp, arms/legs or eyebrows), brittle, split or thinning nails and periostitis have been reported [46]. Most of these effects are reversible and disappear after treatment discontinuation.

In the case of voriconazole hypersensitivity a desensitization with isavuconazole could be contemplated [123].

4.6.1.3 Isavuconazole

Isavuconazole presents a similar type of side effects than voriconazole. However, a RCT on IA showed a better safety profile, with significantly less hepatobiliary, eye and skin disorders, leading to a reduced need for treatment discontinuation [120]. Isavuconazole is safe in patients intolerant to other triazoles [124].

In CPA, long-term toxicities were also compared to voriconazole [125]. Patients treated with isavuconazole presented a significantly lower incidence of side effects (60% vs. 86%, P=0.002), although the rate of discontinuation was similar (50% vs. 52%, P=0.64). The most common isavuconazole associated side effects were neurotoxicity, hepatotoxicity, and skin related toxicity. Another study demonstrated that reasons for isavuconazole discontinuation were mainly hepatotoxicity, neuropathy and malaise, headache, weight loss, confusion, nausea, photosensitivity or dysgeusia [90]. The daily dose rather than plasma levels was predictive of more serious side effects, so a dose reduction could be considered in those with safety concerns.

4.6.1.4 Posaconazole

Posaconazole's main associated side events are gastrointestinal disorders, hypokalemia and pyrexia [37]. Pseudo-hyperaldosteronism may occur, especially in older patients and those with previous hypertension [126]. Patients with pseudo-hyperaldosteronism presented higher plasma levels (3.0 vs. 1.2 mg/L). Of interest, all patients achieving levels ≥4 mg/L were diagnosed of this syndrome. Posaconazole may also lead to hepatotoxicity, with plasma levels >1.83 mg/L being correlated with grade 3 or 4 liver toxicity [127]. In a recent RCT on IA, intravenous and tablets formulations of posaconazole were better tolerated than voriconazole [128].

Oral suspension is associated with a higher risk of headache, dry mouth, peripheral neuropathy and dizziness than tablets [36]. In cases of severe peripheral neuropathy and symptom persistence despite drug withdrawal, treatment with methylprednisolone and magnesium could be considered [129].

4.6.2 L-AmB

L-AmB is better tolerated than other polyenes, presenting the lowest incidence of either infusion-related reactions or nephrotoxicity [18,22,23]. Infusion-related reactions (fever, rigors, headache, arthralgia, nausea, vomiting and hypotension) may occur early during administration (2-6 hours). Providing premedication (hydrocortisone, antihistamine agents, acetaminophen) may prevent these effects, although no evidence of clinical benefit with their routine use is present [23]. Another possible strategy consists of prolonging administration for at least 4 hours [23,130].

L-AmB is associated with a complement activation-related pseudo allergy, which is a type 1 hypersensitivity reaction [23,131]. This reaction may be due to the liposome rather than to the drug *per se* [22]. Unlike infusion-related reactions, it may occur within 5 minutes of infusion and consist of dyspnea, chest pain, back pain, hypoxia, abdominal, flank or leg pain, flushing and urticaria [23]. It normally resolves after either drug discontinuation or the administration of an antihistamine. It is also milder or disappears after repeated exposure [23]. Desensitization to L-AmB could be considered [132].

Risk factors for L-AmB-induced nephrotoxicity include pre-existing decreased intravascular volume, hyponatremia, hypokalemia and congestive heart failure [23]. A recent study showed that concomitant treatment with catecholamine; prior use of angiotensin-converting enzyme inhibitors, angiotensin receptor blockers or carbapenems; concomitant treatment with immunosuppressants and a L-AmB dosage ≥3.52 mg/kg/q24h were independent risk factors of nephrotoxicity [133]. To decrease the risk of renal injury, administering 500-1000 mL of normal saline immediately before and after L-AmB infusion could be considered [23]. In patients in whom this volume may be problematic, a 24-hour infusion is another potential alternative [23]. L-AmB may cause hypokalemia and hypomagnesemia, so monitoring is recommended at least biweekly [23,46]. Due to the potential development of anemia, complete blood count monitoring is warranted on a weekly basis [46]. L-AmB may also lead to liver injury, although it rarely requires treatment discontinuation [24].

Nebulized AmB may increase the risk of bronchospasm [134,135]. Patients diagnosed with ABPA may face a higher risk due to their underlying diseases (bronchiectasis/cystic fibrosis)[134,135]. The first dose should, therefore, be administered in a hospital setting [135]. L-AmB may also be safer than D-AmB within this setting [63,136]. A murine model showed that, unlike L-AmB, D-AmB could inhibit surfactant function [137]. Cholesterol and liposomal phospholipids may account for this difference, given similar properties to pulmonary surfactant [138].

4.6.3 Echinocandins, rezafungin

Echinocandins do not present cross-reactivity with mammalian cells, explaining the excellent tolerability [24,29]. All of the members share the same side effects, presenting a more favorable safety profile than other antifungals [28,29,46].

Echinocandins may cause hepatotoxicity, but it rarely requires treatment discontinuation [29]. Infusion-related reactions consist of rash, facial flushing, swelling, fever, pruritus, hypotension, bronchospasm and angioedema [29,46]. Although all echinocandins may cause this side effect, it is more prevalent with anidulafungin, especially when administered too fast [29,139]. If these reactions occur, supportive care, including a slower infusion rate, is recommended. Infusion rates should be strictly controlled to prevent such onset as follows: anidulafungin at a maximum 1.1 mg/min (a LD in 3 hours and MD in 1.5 hours); caspofungin with a LD and MD in 1 hour; and micafungin in 1 hour [29,140,141]. Other potential side effects include injection site pain or phlebitis (which may be more prevalent with caspofungin) [28,46]. Regarding allergies, these drugs may show cross-reactivity [142].

New antifungals remain in an early stage of study, so knowledge about their safety is limited. To date, rezafungin was well tolerated, with side effects mainly consisting of infusion-related reactions [33].

Ibrexafungerp mainly caused gastrointestinal (diarrhea, abdominal cramps, nausea) effects, followed by headache, dizziness or fatigue [31]. Olorofim acts selectively against fungal DHODH, with differential inhibition activity (2000-fold less potent) on the mammalian enzyme, explaining perhaps its favorable safety profile [1,17]. Dizziness and infusion-related relations appeared to be its most prevalent side effects [32]. Fosmanogepix was well tolerated in Phase II RCT, with headache being the primary side effect [71].

5. Conclusions

The pharmacological management of antifungal agents in patients with different forms of pulmonary aspergillosis represents a challenge for clinicians. Choosing the most appropriate antifungal; optimizing its dose, interval, route of administration, length of treatment; and preventing side effects are essential in boosting efficacy and reducing the risk of associated toxicities. Recently approved drugs have undergone important advances to maximize their use. Likewise, new treatments in development have aimed to solve some problems associated with older drugs. However, much work remains to be done to enhance treatment of this complex disease.

6. Expert Opinion

The increase in immunocompromised patients (primary immune deficiency, solid organ transplantation, cancer chemotherapy and other immunosuppressive drugs, hematopoietic cell transplantation, HIV/AIDS, critically ill, COPD or advanced age) has risen the risk of pulmonary aspergillosis, although invasive fungal infections remain underappreciated and underfunded [1,17]. It is, therefore, integral to improve and optimize the pharmacological management of antifungal agents.

However, this type of management is demanding. Patients diagnosed with different forms of pulmonary aspergillosis are complex, and antifungal agents can give rise to many problems. Similarly, azole resistance is an emerging threat, being associated with higher mortality [37,143]. For example, the prevalence of azole resistance has reached 30% in some European regions; although, in Spain, it remains at 4.7% [1,144]. In this review, we aimed to update all of the information on the pharmacology of various antifungal agents and provide management recommendations for daily clinical practice scenarios to increase the likelihood of better clinical outcomes and reduce the risk of toxicity.

In recent years, treatments for pulmonary aspergillosis have undergone significant improvements. New compounds or formulations have been approved from families already commercialized, while an important variety of novel antifungals with breakthrough properties and mechanisms of action have been developed [17].

Among triazoles, molecules like isavuconazole or formulations such as posaconazole delayed-release tablets or SBA-itraconazole have come to light. These drugs improve both the pharmacokinetics and safety of already

available triazoles, with isavuconazole and posaconazole allowing for more convenient once-a-day dosing. However, in invasive aspergillosis, these two drugs did not significantly improve clinical outcomes, and mortality remains similar to that of voriconazole [120,128,145]. In other forms of pulmonary aspergillosis, data remain scarce. Although isavuconazole and posaconazole have shown to be safer than voriconazole in invasive aspergillosis, use of such drugs is still limited in other forms of pulmonary aspergillosis, such as chronic pulmonary or allergic bronchopulmonary aspergillosis, given the high costs and small number of studies done [120,128].

In the case of polyenes, new lipid formulations greatly improve the safety of previous forms. However, they continue to serve as alternative agents, given the associated side effects and need for intravenous infusion. Their use by nebulized route is another interesting, possible choice, especially in either patients intubated or with aspergilloma. More studies are, however, needed to determine efficacy and safety.

With respect to new agents, rezafungin, ibrexafungerp, olorofim and fosmanogepix extend the spectrum of available drugs against difficult-to-treat cryptic species and azole-resistant strains. These agents present important improvements in PK, drug-drug interactions and safety. Nevertheless, their development is still early-stage. Results from clinical trials remain to be published to determine both positioning of these agents in the treatment of pulmonary aspergillosis and their potential utility when combined with other agents already available.

The different areas of antifungal agent pharmacology present important drawbacks that must be acknowledged. In terms of pharmacokinetics, drug penetration evidence mainly comes from murine models, human volunteers or patients with conditions different that those found in daily clinical practice. For this reason, caution is advised when interpreting results. Drug penetration in patients suffering from lung aspergillosis may differ from healthy volunteers due to altered permeability or tissue structure secondary to tissue necrosis or biofilm formation [146]. For example, a murine model showed an accumulation of posaconazole within necrotic tissue, with up to 38 % higher levels compared to those found in unaffected tissue [146]. Furthermore, results based on tissue/cell/plasma ratio should also be interpreted with caution. As these drugs have a high binding to albumin, results from plasma levels should be detailed. This ratio could change dramatically, being either low if total plasma concentrations are considered or higher if only unbound drug concentrations are described [147].

Concerning pharmacodynamics, many limitations are also present [37]. Firstly, PK/PD indices are mostly based on animal studies. Secondly, whereas MIC is a static concentration performed in predetermined and stable conditions (temperature, pH, and antifungal concentration), data on the impact of dynamics of *in vivo* exposure are still scarce. Thirdly, these murine models do not normally consider the potential effect of immunity in fungal infection, which may decrease the required *in vivo* exposure in immunocompetent

individuals and vice versa. Finally, the post antifungal effect is a concept that has yet to be appropriately assessed and for which the clinical impact remains unknown.

Additionally, dosage recommendations are another determining point in care. Patients diagnosed with pulmonary aspergillosis present special characteristics that complicate dosing. Although TDM is routinely recommended, it may not be always available. Conversely, if available, results during TDM may take some time to arrive. Thus, clinicians must make decisions regarding dosing without considering TDM. Whereas data on obesity or critically ill patients are available for some antifungals (although, of limited quality since most come from case reports) information on dosage recommendations in patients with cachexia or hypoalbuminemia is scarce. However, this insight is extremely important and relevant, given the protein binding of most antifungal agents and the risk of plasma drug concentrations alterations entailed. Similarly, available information related to dosing and TDM in other forms such as chronic pulmonary or allergic bronchopulmonary aspergillosis is limited. Patients diagnosed with these forms will vary from those with invasive aspergillosis. More data are needed on therapeutic goals and appropriate dosing in this series of patients, especially as they experience prolonged treatment and have high rates of side effects.

Lastly, safety is a main factor that determines therapy management. Main side effects are well-known and have improved with the introduction of new drugs like isavuconazole or posaconazole. TDM plays a fundamental role in preventing the development of toxicities. With new antifungals, including olorofim and fosmanogepix, presenting fungal-specific targets, the risk of toxicity caused by these molecules is lower [17].

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Table 1. Clinical use of antifungal agents in the different forms of pulmonary aspergillosis.

Ref.	Itraconazole	Voriconazole	Isavuconazole	Posaconazole	Liposomal amphotericin B	Echinocandins (anidulafungin, caspofungin, micafungin)	Length of treatment
IA [18,55,120,128]	Not recommended	First line	First line	First line	Alternative first-line agent	Only in combination (initial therapy, azole resistance or salvage therapy)	6-12 weeks
CPA [8,148]	First line	Second line*	Third line	Third line	If therapy with triazoles not possible (intolerance, resistance)		At least 6 months
ABPA [9]	First line, with or without corticosteroids	Second line	Third line	Third line			4 months
					Nebulized: in de-vascularized sites, intubated patients, or patients with concomitant mycobacterial infection *Percutaneous intracavitary instillation:* in CPA and aspergilloma		

IA: invasive aspergillosis; *CPA:* chronic pulmonary aspergillosis; *ABPA:* allergic bronchopulmonary aspergillosis.

* Preferred to itraconazole for large aspergillomas or more severe forms, including bilateral extension or subacute invasive aspergillosis.

Table 2: Pharmacokinetics of antifungal agents approved and in development for the treatment of pulmonary aspergillosis.

Drug and ref.	Formulation	Oral Bioavailability (%)	Oral administration	Nasogastric tube	*V* (L/kg)	PPB (%)	ELF/ plasma	Alveolar macrophage/ plasma	Lung tissue/ plasma	Half-life (h)	Renal excretion (%)	PK/PD index
Itraconazole [35,38,39,44,48,149,150]	*OR:* (capsule, solution, SBA) *IV*	55 (greater with the solution)	*Capsule:* Food/acidic beverages *Solution:* Fasting *SBA:* Food/fasting	Solution	11	99.8	0.3	2-5	0.9-7	34	< 1	AUC/MIC ≥25
Voriconazole [14,21,39,44,47,48,55,72,73]	*OR:* (tablet, solution), *IV*	96	Fasting	Solution	4.6	58	6-12.5	3.8-6.5	0.3-3.2	6-7	< 2	
Isavuconazole [19,20,44,48,151]	*OR:* (capsule), *IV*	98	Food/fasting	Capsule	5.6	99	NA	NA	2.7	110-130	< 1	
Posaconazole [36,37,39,44,152]	*OR:* (tablet,	54	*Tablet:* Food/fasting	Tablet	7-25	99	0.6-1.2	30-42.6	0.9-20	20-31	< 1	

	solution), *IV*		*Solution:* High fat meal (50 g)									
L-AmB [22,39,44,48,60,153]	*IV*	< 5	-	-	1.8-2.3	NA	0.08-5	0.3	0.2-2.5	152	4.5	C_{max}/MIC> 40
Anidulafungin [27–29,39,44,48]	*IV*	< 5	-	-	0.4-0.6	84-98	0.5-5	14	10	24	< 1	AUC/MEC 10-20
Caspofungin [27–29,39,44,48,102]	*IV*	< 5	-	-	0.1	97	NA	5	1.1	27-50	2	
Micafungin [27–29,39,44,48]	*IV*	< 5	-	-	0.4	99	1.1-6.2	4	2.8	15-17	< 1	
Rezafungin [17,44,66,68,74,154,155]	*IV, SC*	< 5	-	-	0.4-0.6	99	0.8	NA	4.3	130-150	< 0.3	
Ibrexafungerp [1,17,31,44,69]	*OR:* (capsule) *IV*	35-51	Meals high in fat	Capsule	4.7-5.3	99.7	5	NA	27-31	20-30	1.5	AUC/MIC

Olorofim [1,17,32,156]	*OR:* (tablet) *IV*	45-82	Fasting	Tablet	2.9-3.5	> 99	NA	NA	NA	20-30	0.2	C_{min}/MIC 9-19
Fosmanogepix [1,17,33,71,157,158]	*OR:* (tablet) *IV*	90	Food/fasting	Tablet	NA	98.3	NA	NA	NA	60	< 1	AUC/MEC >5,258

PPB: Plasma protein binding; *ELF:* epithelial lining fluid; *PK/PD*: Pharmacokinetics/pharmacodynamics; *OR:* oral; *SBA:* super bioavailability; *IV:* intravenous; *AUC:* area under the curve; *MIC:* minimum inhibitory concentration; *L-AmB:* liposomal amphotericin B; *NA:* not available; C_{max}*:* maximum plasma concentration; *SC:* subcutaneous; *MEC*: minimum effective concentration; C_{min}*:* minimum plasma concentration.

Table 3. Spectrum and activity of antifungal agents against *Aspergillus* spp.

Ref.	Drug	*A. fumigatus*	*A. flavus*	*A. niger*	*A. terreus*	*A. nidulans*	*A. lentulus*
[159,160]	**Itraconazole** [159,160]	✓	✓	✓	✓	✓	-
[159,160]	**Voriconazole** [159,160]	✓✓	✓✓	✓✓	✓✓	✓✓	-
[159,160]	**Isavuconazole** [159,160]	✓✓	✓✓	✓✓	✓✓	✓✓	-
[37,159,160]	**Posaconazole** [37,159,160]	✓✓	✓✓	✓✓	✓✓	✓	-
[55,159,160]	**Amphotericin B** [55,159,160]	✓✓	-	✓✓	-	-	-
[28,159]	**Echinocandins** [28,159]	✓	✓	✓	✓	✓	✓✓*
[17]	**Rezafungin** [17]	✓	✓	✓	✓	✓	✓
[31]	**Ibrexafungerp** [31]	✓✓	✓✓	✓✓	✓✓	✓✓	✓✓
[5,17,32]	**Olorofim** [5,17,32]	✓✓	✓✓	✓✓	✓✓	✓✓	✓✓
[1,71]	**Fosmanogepix** [1,71]	✓✓	✓✓	✓✓	✓✓	✓✓	✓✓

✓✓: highly active, recommended; ✓: moderate activity; -: inactive or decreased activity, not recommended.

* *A.lentulus* is susceptible to micafungin and anidulafungin, albeit not caspofungin [28].

Table 4. Antifungal dosing recommendations, including those for special populations.

Drug	Standard dosing		Special situations						
	IA	CPA, ABPA	Obese	Renal impairment			ECMO	Hepatic impairment	
				GF < 50 mL/min	HD	CRRT		*Child Pugh*	
						CVVH / CVVHDF		A/B	C
Itraconazole [24,38,47,55,73,81,102,113,130]	*IV:* Day 1-2: 200 mg q12h Day 3: 200 mg q24h *OR:* 200 mg q12h SUBA: 130 mg q12h	*OR:* 200 mg q12h	Standard	*IV:* Not recommended *OR:* Standard	Standard	Standard / 300 mg q24h	Standard	Standard	
Voriconazole [21,24,121,130,161,47,55,73,87,88,102,107,108]	*IV:* Day 1: 6 mg/kg q12h Day 2: 4 mg/kg q12h * *OR:* Day 1: 400 mg q12h Day 2: 200 mg q12h// Day 1: 6 mg/kg q12h Day 2: 4 mg/kg q12h *	*OR:* 150-200 mg q12h	ABW	*IV:* Not recommended *OR:* Standard	Standard	Standard	Increase dose	Day 2: 50 % reduction	Day 1: 200 mg q12h Day 2: 50 mg q12h or 100 mg q24h
Isavuconazole [19,47,55,73,81,90,91,162,163]	*IV/OR:* Day 1-2: 200 mg q12h Day 3: 200 mg q24h	Day 1-2: 200 mg q12h Day 3: 100-200 mg q24h	Standard	Standard	Standard	Standard	Standard	Standard	
Posaconazole [24,37,47,54,55,102,152]	*IV, OR (tablets):* Day 1: 300 mg q12h Day 2: 300 mg q24h *OR (solution):* 200 mg q6h (if no meals), 400 mg q12h (fatty meals)	*OR (tablets):* 200-300 mg q24h 400 mg q12h	*IV:* 120-170 kg: 400 mg q24h > 170 kg: 500 mg q24h	*IV:* Not recommended *OR:* Standard	Standard	Standard	Standard	Standard	

L-AmB [22,24,59,91,102,164]	3 mg/kg q24h	*IV*: Standard *Neb:* 25-50 mg q12h-24h ** *PII:* 50 mg q24h	> 100 kg: 300 mg q24h	Standard	Standard	Standard	Increase dose	Standard	
Anidulafungin [24,27,28,47,73,81,102,165]	LD: 200 mg MD: 100 mg q24h	-	> 140 kg: increase 25 % LD/MD	Standard	Standard	Standard	Standard	Standard	
Caspofungin [24,27,28,47,81,102,104]	LD: 70 mg MD: 50 mg q24h	50-70 mg q24h	150 mg q24h	Standard	Standard	LD: 100 mg	MD: 70 mg q24h	*B:* MD: 35 mg q24h∞	Standard
Micafungin [24,27,28,47,81,102,105]	100 mg q24h	150 mg q24h	¥	Standard	Standard	150-200 mg q24h	200 mg q24h	Standard	

IA: invasive aspergillosis*; CPA:* chronic pulmonary aspergillosis*; ABPA:* allergic bronchopulmonary aspergillosis*; GF:* glomerular filtration*; HD:* hemodialysis*; CRRT:* continuous renal replacement therapy; *CVVH:* continuous veno-venous hemofiltration; *CVVHDF:* continuous veno-venous hemodiafiltration; *ECMO:* extracorporeal membrane oxygenation; IV: intravenous; *OR:* oral; *ABW:* adjusted body weight; *L-AmB:* liposomal amphotericin B; *Neb:* nebulized; *PII:* percutaneous intracavitary instillation; *LD:* loading dose; *MD:* maintenance dose.

* If < 40 kg, reduce dose by 50 % [121]. If clinical response is inadequate, consider an increase to OR 300 mg q12h or 150 q12h when patient is < 40 kg [121].

Off-label use has been reported, with some clinicians opting to prescribe oral dosing as intravenous dosing, especially in severe infections [166].

** *Neb:* 25-50 mg in 6 mL of sterile water. Administer through a jet nebulizer. Caution: in ventilated patients, AmB may precipitate in the breathing tube, especially if hypertonic nebulized saline is concomitantly administered. In ABPA or severe asthma fungal sensitization, 25 mg twice weekly followed by a MD of 25 mg weekly for 6 months is recommended [167]. *PII:* 50 mg in 20 mL dextrose 5 %.

∞: Consider a dose reduction to 35 mg in MD if patient is not critically ill.

¥ Dose (mg) = weight (kg) + 42 [81].

Table 5. Therapeutic drug monitoring recommendations for triazoles.

Drug	TDM timepoint	Goal trough levels (mg/L) [55]
Itraconazole	7	1-4* (HPLC) 3-17 (Bioassay)
Voriconazole	2-5	1-5.5**
Isavuconazole* **	5	1-3
Posaconazole	7	> 1-3.75

TDM: therapeutic drug monitoring; *HPLC:* high performance liquid chromatography.

* Bioassay measures both itraconazole and hydroxy-itraconazole; HPLC measures itraconazole and hydroxy-itraconazole separately. Both compounds present different antifungal activity. Itraconazole monitoring alone may be preferred [45].

**In patients with severe disease, high minimum inhibitory concentrations or diseases with poor prognosis (central nervous system infection, bulky disease, multifocal or disseminated infections), a higher trough value (2 mg/L) is recommended [47].

*** Only recommended in certain situations: treatment failure, toxicity, non-compliance, obese, receiving concomitant medications that are predicted to reduce isavuconazole concentrations, hepatic failure, age < 18 years, pathogen infections with high minimum inhibitory concentrations [24,55,112].

Figure 1. Mechanisms of action of the different antifungals.

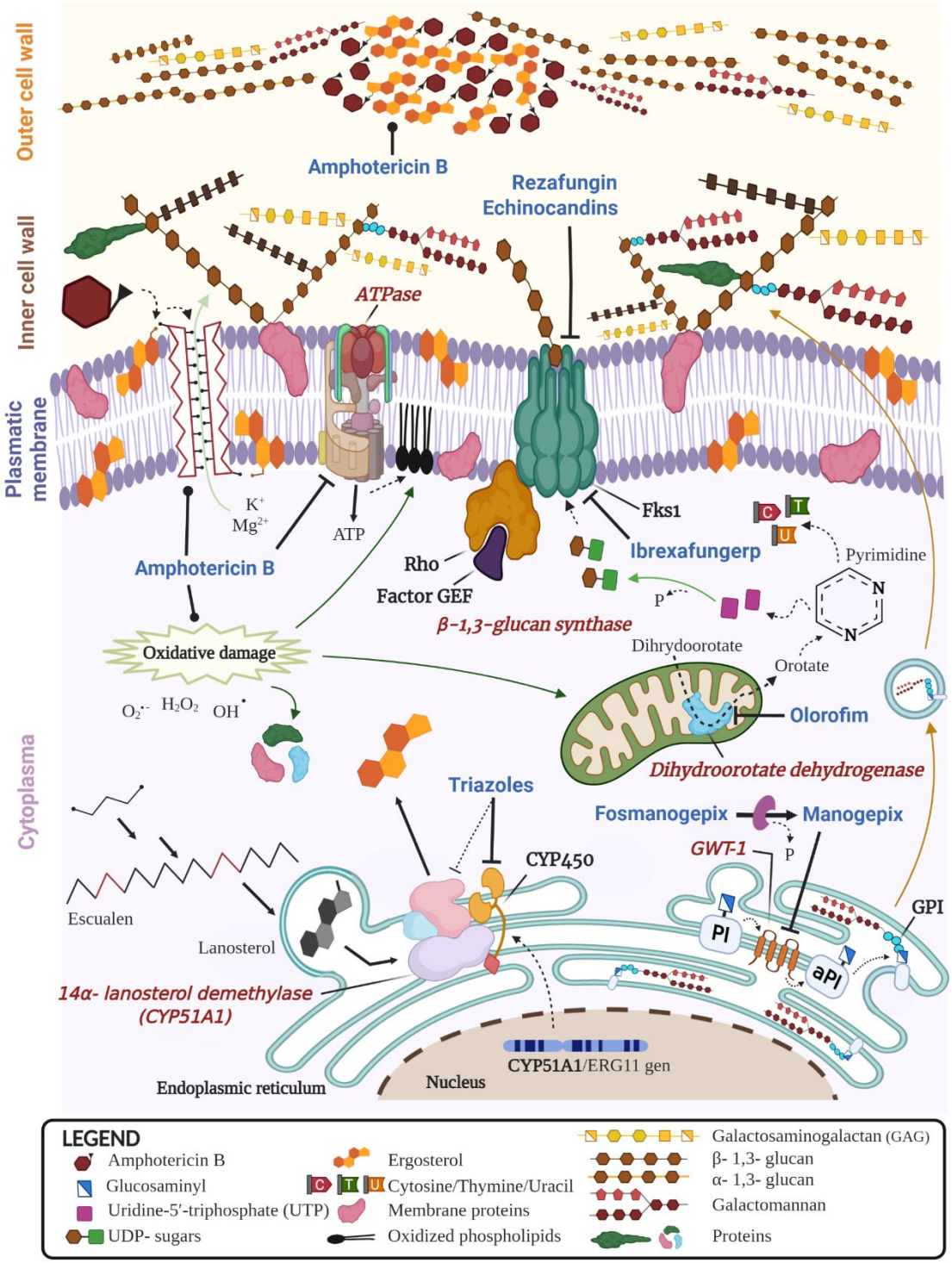

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Figure 2. Summary of the main adverse effects of antifungals.

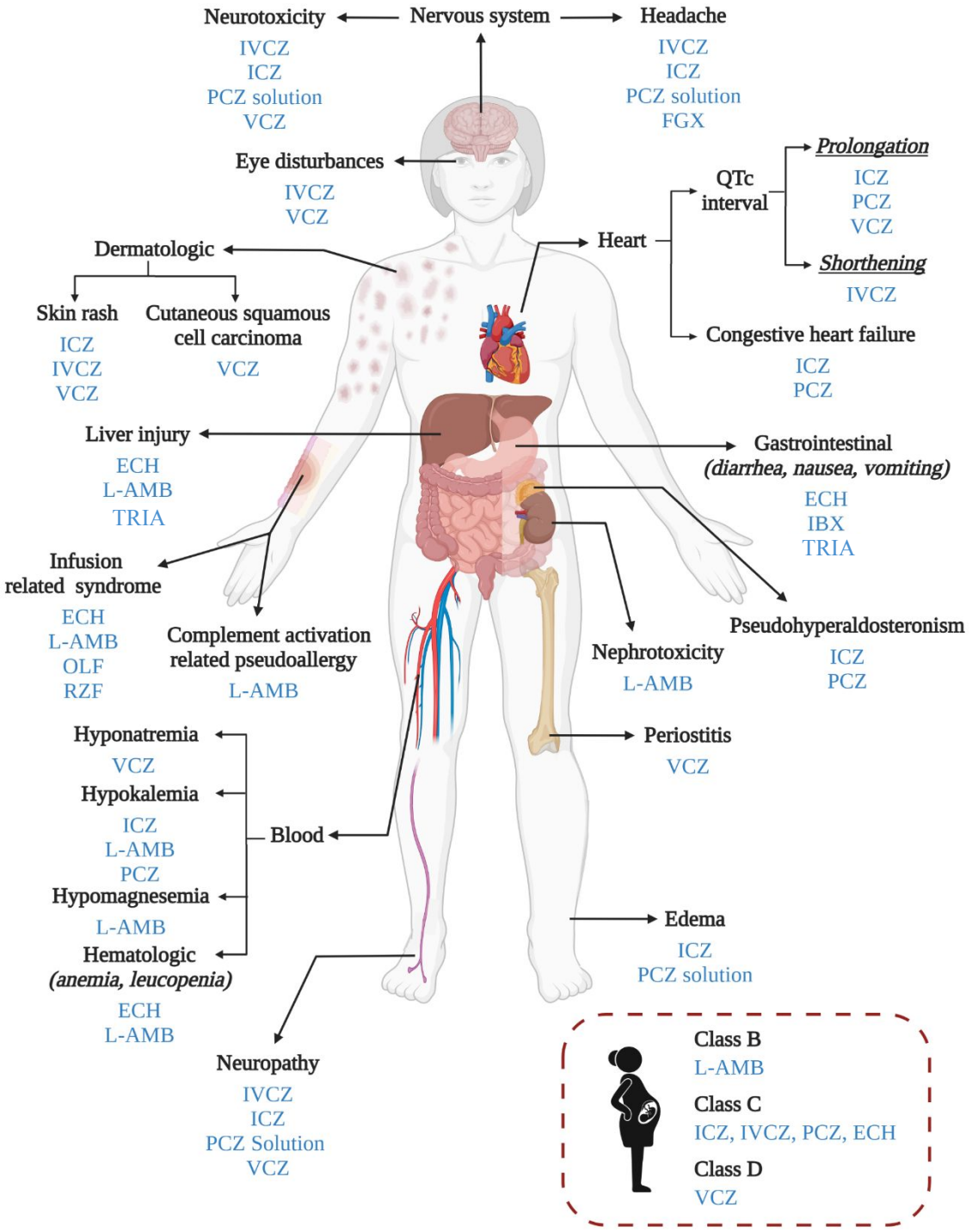

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Figure legends. ECH: echinocandins; FGX: fosmanogepix; IBX: ibrexafungerp; ICZ: itraconazole; IVCZ: isavuconazole; L-AMB: liposomal amphotericin B; OLF: olorofim; PCZ: posaconazole; RZF: rezafungin; TRIA: triazoles; VCZ: voriconazole. Pregnancy risk was defined according to US FDA (131).

Supplementary material

1. *Data sources*

The following search terms were included: invasive aspergillosis (IA), aspergilloma, chronic pulmonary aspergillosis (CPA), allergic bronchopulmonary aspergillosis (ABPA), antifungal, triazoles, itraconazole, SUBA-itraconazole, voriconazole, isavuconazole, posaconazole, polyenes, liposomal amphotericin B (L-AmB), echinocandins, micafungin, anidulafungin, caspofungin, rezafungin, ibrexafungerp, olorofim, fosmanogepix, pharmacokinetics (PK), drug-drug interactions (DDI), pharmacodynamics (PD), post-antifungal effect (PAFE), fungicidal, fungistatic, safety, obesity, cachexia, pregnancy, total renal replacement therapies (TRRT), extracorporeal membrane oxygenation (ECMO), hematologic malignancy, critically ill, hepatic impairment, nasogastric tube, hypoalbuminemia, therapeutic drug monitoring (TDM), side effects, allergy, desensitization. Excellent reviews on the upcoming drugs in the treatment of aspergillosis have been recently published and will only be briefly summarized [1–5]. Among novel drugs, only those in Phase II and Phase III randomized clinical trials (RCT) were included. We restricted the search to adult (> 18 years old) patients and treatment of pulmonary aspergillosis, excluding data on prophylaxis.

2. *Mechanisms of resistance*

2.1 Triazoles

The main mechanism of resistance is due to mutations in the CYP51, notably in the *CYP51a* and *CYP51b* genes [6]. Other mechanisms include the expression of efflux pump proteins [7]. Although most resistance mutations affect the susceptibility of all azoles, some exceptions should be stated. TR_{34}/L98H is normally itraconazole resistant, with variable activity of voriconazole, isavuconazole and Posaconazole [8]. On the other hand, TR46/Y121F/T289A normally show high resistance to voriconazole and isavuconazole, whereas posaconazole and itraconazole are usually less affected [8].

2.2 L-AmB

The mechanism of resistance is not fully understood. The existence of mutants with low levels of ergosterol, disturbances in the composition of membrane phospholipids, the presence of higher than normal levels of antioxidative enzymes and/or alterations in the production of free radicals may account for the resistance to this polyene [9].

2.3 Echinocandins

Although not common, the specific mutations in the *FKS1* gene are responsible for the resistance to this family [10,11]. Other mechanisms include the cell response to stress [10]. The decrease in β-(1,3)-D-glucan induces the activation of adaptive mechanisms to protect the cell, which includes an increase of chitin production or

calcineurin pathway [10,11]. As a result, *Aspergillus* spp. may also show tolerance to echinocandins through maintaining residual growth [12].

3. Pharmacokinetics

The most relevant DDI and their management have been summarized in Table S1.

3.1 Comparation of L-AmB with other polyenes

Compared to other formulations, L-AmB presented a higher penetration in epithelial lining fluid (ELF) than amphotericin B lipid complex (ABLC) or deoxycholate-amphotericin B (D-AMB)[13], with higher and sustained plasmatic concentrations [13]. ABLC showed higher levels in the lung tissue and pulmonary alveolar macrophages [13]. Although the greater tissue penetration of ABLC, clinical efficacy of both formulations is similar [14]. A rabbit model (which show similar PK and anatomical barriers than humans, therefore allowing to extrapolating the data) assessed the pulmonary concentration in different compartments after 8 days of daily dosing [13]. In this study, L-AmB presented a higher penetration in ELF (2.28 µg/mL vs. 0.90 µg/mL with ABLC or 0.44 µg/mL with D-AMB), whereas ABLC levels were higher in the lung tissue (16.3 µg/g vs. 6.32 µg/g with L-AmB or 2.71 µg/g with D-AMB) and pulmonary alveolar macrophages (89.1 µg/mL vs. 7.5 µg/mL with L-AmB or 8.9 µg/mL with D-AMB [13]. In plasma, L-AmB was the formulation with the highest concentrations (26.4 µg/mL vs. 0.24 µg/mL with ABLC or 0.34 µg/mL with D-AMB)[13]. Differences in lung penetration may be related to the anatomical site. Higher penetrations of L-AmB into ELF are probably associated with a higher drug concentration gradient across the barrier between blood and alveolar space [13]. ABLC, which presents a higher volume of distribution than L-AmB, preferentially distributed to alveolar macrophages, with a higher lung tissue concentration present as a consequence of the fraction of macrophages that remained in the tissue [13]. The main reason of differences in plasmatic concentrations is that depending on the formulation, amphotericin B (AMB) is more rapidly taken up by mononuclear phagocytic system (ABLC) or has a more prolonged circulation in the bloodstream (L-AmB)[13].

4. Pharmacodynamics

Antifungals show two different activity patterns: concentration-dependent and time-dependent [15]. For those showing concentration-dependent activity, the fungal killing increases as the antifungal concentration is heightened [15]. On the contrary, drugs with time-dependent activity are characterized by a maximal activity when concentrations are above the minimum inhibitory concentration (MIC) during the administration interval [15].

PD indexes which best describe the concentration-dependent antifungals are the maximum plasma concentration (C_{max})/MIC and the area under the curve (AUC)/MIC. Otherwise, the time (expressed as a

percentage of the dosing interval) that free drug concentrations are above the MIC (*f*%T>MIC) is the PD index which better describes the time-dependent activity [15].

Different fungicidal and fungistatic descriptions have been used to define lethal activities from antifungals on *Aspergillus* species [16,17]. Unfortunately, the clinical implications of these definitions are unknown, as they present several limitations. Firstly, : some of them have being extrapolated from bacteria definitions; secondly, *in vitro* evidence suggests that this behavior is more species-dependent rather than drug-dependent [17].

One important issue that has not fully been elucidated is PAFE. This effect is defined as the time required for the fungal cell to recover from the transient crippling injury sustained by the organism as a result of an exposure to the antifungal drug [18,19]. It depends on the time of action, time of exposure and stage of cellular growth. Triazoles do not exhibit a significant PAFE. Itraconazole did not induce PAFE in any of the *Aspergillus* species tested, even at concentrations as high as 50xMIC [20]. Voriconazole presented a time dependent short PAFE of 2.73 hours at concentrations 2.5-40xMIC, with a slight concentration effect [21]. When 4 hours exposure were studied, a short PAFE of 0.53 hours was detected [21]. This PAFE (0.5-0.75 hours) was also seen in other studies [19]. Posaconazole did not present a significant PAFE (0.75 ± 0.35 hours) either.[19] In these studies, a relatively short time of exposure was assessed [19]. This is one of the main reasons behind the lack of PAFE with triazoles in some studies, as they may need a longer exposure to deplete the lanosterol in the fungal cell (12-24 hours to kill more than 90% of the cells)[19]. L-AmB exhibits a rapid PAFE of 2.6-15.3 hours at concentrations 1-10xMIC [21]. This phenomenon was only seen against *A. fumigatus* [20]. The mechanism of action of polyenes may account for these differences with triazoles, , as they can rapidly act after a short exposure (2 hours)[19]. Echinocandins do not show a significant PAFE (≤0.5 hours), probably because they do not exert permanent injury to the cell [19].

Caspofungin may show a “paradoxical effect”. *Aspergillus spp.,* in response to stress, induces the activation of adaptive processes to protect the cell [10,11]. This is achieved through the increase in intracellular calcium [12], which activates the calmodulin, chitin or calcineurin pathway in the presence of high concentrations of caspofungin to compensate the loss of β-(1,3)-D-glucan [10–12].

5. Posology

Obesity is a worldwide concern that influences on drug exposure of antifungals, owing their high lipophilicity [22,23]. Obesity can affect PK and PD properties due pathophysiological changes and increase in fat tissue mass [24–26]. Drug distribution depends not only on the lipophilicity of the drug, resulting in a higher *V*, but also to the protein binding since these patients have an elevated cholesterol and triglyceride concentrations that can affect drugs which are extensively bind to plasma proteins, such antifungals [26]. Derived from this scenario, it is expected that some antifungals drugs will be underdosed and may not reach therapeutic

concentrations. On the other hand, in hydrophilic drugs, adjusted body weight may be more appropriate that total body weight to avoid the risk of toxicity [22,25,27].

On the contrary, patients with underweight and cachexia may also develop pulmonary aspergillosis, especially CPA. These patients present different alterations in their body composition which may play a role in antifungal concentrations. Cachexia is a weight-loss process that leads to changes in the body structure and function, which may influence PK of different drugs [28]. These patients present a lower adipose tissue amount, leading to a reduction of the volume of distribution of lipophilic drugs [28]. Cachectic patients can also present an impaired metabolism, which could imply a higher exposure to drugs highly metabolized by liver.[28] Consequently, if dosed on a standard basis, these features could lead to a higher risk of supratherapeutic concentrations and side effects of most antifungals given their lipophilicity and liver metabolism. Unfortunately, evidence of the appropriate management in these patients is lacking.

In patients with renal impairment, both intermittent hemodialysis (IHD) or continuous renal replacement therapy (CRRT) can be employed [29]. Both techniques can impact on a different manner on the PK of drugs. So far, the reduced doses recommended in IHD could be low during CRRT, especially when hydrophilic drugs are used [29]. Several factors take part in the potential CRRT-related elimination [29]: *antimicrobial characteristics*: molecular weight, plasma protein binding, hydro- or lipophilicity and *CRRT parameters:* membrane sieving coefficient or adsorption capacity [29]. Hemofilters can extract antifungal drugs through three mechanisms: diffusion across the membrane; trapping of the drug in areas of stasis and direct adsorption [30]. The hypoalbuminemia present in critically ill patients may increase the fraction of unbound drug which may bring a higher risk of hemofilter direct adsorption [30].

The high protein binding and non-renal elimination may explain the lack of dose adjustment requirement for most antifungals in patients with IHD or CRRT [31]. However, in some circumstances, the increase in the volume of distribution derived from these techniques, especially at the beginning, coupled with the severity of patients may warrant an increase in the dose of some of them [32].

Hypoalbuminemia is a common finding in patients with fungal disease that may significantly affect drug exposure, especially in the critically-ill [33]. Hypoalbuminemia can alter the PK of highly-bound drugs which [34]. Low serum albumin levels may increase free drug concentrations, which may increase/decrease liver clearance due to the hepatic metabolism of most antifungals, leading to sub/supra-therapeutic concentrations [33]. The higher proportion of free drug could lead to a higher penetration in other compartments, such as CNS, potentially increasing the risk of suffering adverse events but also reaching therapeutic concentrations to treat severe infections [35].

The use of extracorporeal membrane oxygenation (ECMO) may alter the PK of different drugs prescribed for critically ill patients, especially those lipophilic and highly protein-bound, like most of the antifungals [36]. This alteration may be a consequence of: increased volume of distribution due to the addition of the large volume of exogenous blood; CRRT, which are common in these patients and the extraction of the drug by components of the circuit [30].

Due to the hepatic metabolism of some of them, pre-existing liver injury may alter the PK increasing the risk of supratherapeutic plasmatic levels [37]. A wide variation on the incidence of hepatotoxicity has been reported, which depends on the type of patients evaluated, dosage, drug interactions, TDM and definitions of drug related liver injury [37].

6. Therapeutic drug monitoring

Due to the PK of antifungals and the particular situation of patients with aspergillosis, the standard dosing recommendations may not achieve effective or safe drug exposures, leading to potential treatment failures or toxicities [38]. For this reason, the performance of routine TDM is advised for most antifungals, especially in the clinical scenarios already described [38,39]. Once the therapeutic goal is achieved, there is no consensus on the periodicity of TDM measurements, but could be considered when any of the clinical scenarios described are present or change [39].

One important issue is that recent evidence suggests that plasma levels may not serve as a reliable surrogate measure of drug exposure at the site of infection, as different PK parameters have been reported for plasma and lung tissues [40]. When possible, levels in the lung should be monitored, although these techniques are not without limitations [40–42].

7. Safety

7.1 Triazoles

Itraconazole and posaconazole may lead to pseudo-hyperaldosteronism. The potential mechanism is the inhibition of 11β-hydroxylase, which results in the accumulation of 11β-deoxycorticosterone and 11β-deoxycortisol, with important mineralocorticoid effects [43]. A negative inotropic effect may also play a role in the development of these toxicities [44]. Voriconazole can cause a phototoxicity-like rash which is thought to be to the metabolite *N-oxide* [44]. Regarding the risk of squamous cell carcinomas (SCC), in the largest cohort of lung transplant recipients, voriconazole use was associated with a higher odds of SCC but not cutaneous basal cell carcinoma [45]. The risk was associated to prolonged use (those with durations of 4-7 months presented an increased risk of 1.42-fold, whereas those treated > 15 months experienced a 3-fold risk increase)[45]. A recent study, however, suggested that these effects may be more related to the concomitant

immunosuppression rather than to voriconazole *per* se, although close monitoring is highly recommended [44,46].

7.2 L-AmB

The main mechanism of infusion related reactions is the activation of Toll-like receptor 2, leading to the release of pro-inflammatory cytokines [47]. This mechanism could also play a role in nephrotoxicity, as the release of TNF-α may increase afferent arteriolar vasoconstriction [47]. The encapsulation of AMB inside a liposome reduces the risk of these side effects due to a lower rate of cytokine liberation [47].

Released AMB from liposomes can also cause direct tubular damage in the kidneys by creating pores [47]. These pores reduce the reabsorption of some electrolytes as magnesium and potassium, leading to the well-known L-AmB associated hypokalemia and hypomagnesemia [47]. Anemia may be due to the suppression of erythropoietin [44].

7.3 Echinocandins

Similar to L-AmB, infusion related reactions may occur as a consequence of the release of histamine [44,48].

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Table S1. Main potential drug-drug interactions of triazoles and their management.

	Voriconazole[49–57]		**Isavuconazole**[58,59]		**Itraconazole**[57,60,69,61–68]		**Posaconazole**[57,70]	
	Effect	Recommendation	Effect	Recommendation	Effect	Recommendation	Effect	Recommendation
Systemic corticosteroids								
Prednisone*	Moderate severity CYP3A4 inhibition: ↑prednisone levels	Monitor for prednisone toxicity If necessary, ↓prednisone dose	↑prednisone levels	No action needed	↑prednisone levels	Monitor for prednisone toxicity If necessary, ↓prednisone dose	↑prednisone levels	Monitor for prednisone toxicity If necessary, ↓prednisone dose
Hydrocortisone	Moderate severity CYP3A4 inhibition: ↑hydrocortisone levels	Monitor for hydrocortisone toxicity If necessary, ↓hydrocortisone dose by as much as 60%	No interaction expected	-	Moderate severity CYP3A4 inhibition: ↑hydrocortisone levels	Monitor for hydrocortisone toxicity If necessary, ↓hydrocortisone dose by as much as 60%	Moderate severity CYP3A4 inhibition: ↑hydrocortisone levels	Monitor for hydrocortisone toxicity If necessary, ↓hydrocortisone dose by as much as 60%
Methylprednisolone**	Moderate severity CYP3A4 inhibition: ↑methylprednisolone levels	Consider switch to prednisone. If necessary, ↓ 50% methylprednisolone dose	Moderate severity CYP3A4 inhibition: ↑methylprednisolone levels	Monitor for methylprednisolone toxicity	Moderate severity CYP3A4 inhibition: ↑methylprednisolone levels	Consider switch to prednisone. If necessary, ↓ 50% methylprednisolone dose	Moderate severity CYP3A4 inhibition: ↑methylprednisolone levels	Consider switch to prednisone. If necessary, ↓ 50% methylprednisolone dose
Dexamethasone	Moderate severity CYP3A4, CYP2C9, CYP2C1 induction: ↓voriconazole levels	Voriconazole TDM, ↑voriconazole doses may be required	Moderate severity CYP3A4 inhibition: ↑dexamethasone levels	Monitor for dexamethasone toxicity	Moderate severity CYP3A4 inhibition: ↑dexamethasone levels	Consider switch to prednisone. If necessary, ↓dexamethasone dose	Moderate severity CYP3A4 inhibition: ↑dexamethasone levels	Consider switch to prednisone. If necessary, ↓dexamethasone dose
Inhaled corticosteroids								
Beclomethasone	Minor severity CYP3A4 inhibition: ↑beclomethasone levels	No action needed	No interaction expected	-	Minor severity CYP3A4 inhibition: ↑beclomethasone levels	No action needed	Minor severity CYP3A4 inhibition: ↑beclomethasone levels	No action needed
Budesonide	Moderate severity CYP3A4 inhibition: ↑budesonide levels	Consider switch to beclomethasone	Minor severity CYP3A4 inhibition: ↑budesonide levels	Consider switch to beclomethasone	Moderate severity CYP3A4 inhibition: ↑budesonide levels	Consider switch to beclomethasone	Moderate severity CYP3A4 inhibition: ↑budesonide levels	Consider switch to beclomethasone
Fluticasone	Moderate severity CYP3A4 inhibition: ↑fluticasone levels	Consider switch to beclomethasone	Minor severity CYP3A4 inhibition: ↑fluticasone levels	Consider switch to beclomethasone	Moderate severity CYP3A4 inhibition: ↑fluticasone levels	Consider switch to beclomethasone	Moderate severity CYP3A4 inhibition: ↑fluticasone levels	Consider switch to beclomethasone
Rifamycins								
Rifampin	Major severity CYP2C19, CYP3A4 induction: ↓voriconazole levels	Avoid combination. Consider switch to posaconazole	Major severity CYP3A4 induction: ↓isavuconazole levels	Avoid combination Consider switch to posaconazole	Major severity CYP3A4 induction: ↓itraconazole levels	Avoid combination Consider switch to posaconazole	Major severity CYP3A4 induction: ↓posaconazole levels	Posaconazole delayed-release tables and TDM
Rifabutin	Major severity CYP3A4 induction and inhibition: ↓voriconazole levels	Avoid combination Consider therapy modification	Major severity CYP3A4 induction and inhibition: ↓isavuconazole levels ↑Rifabutin levels	Isavuconazole TDM and monitor for rifabutin toxicity	Major severity CYP3A4 induction and inhibition: ↓itraconazole leves ↑Rifabutin levels	Itraconazole TDM and monitor for rifabutin toxicity	Major severity CYP3A4 induction and inhibition: ↓posaconazole levels ↑ rifabutin levels	Posaconazole delayed-release tables and TDM

	↑Rifabutin levels							
Oral anticoagulants								
Warfarin	Moderate severity CYP2C9 inhibition: ↑Warfarin levels	INR should be monitored within 1 week of onset	No interaction expected	-	Moderate severity CYP2C9 and CYP3A4inhibition: ↑Warfarin levels	INR should be monitored within 1 week of onset	Moderate severity CYP3A4 inhibition: ↑Warfarin levels	INR should be monitored within 1 week of onset
Acenocumarol	Moderate severity CYP2C9inhibition: ↑acenocumarol levels	INR should be monitored within 1 week of onset	No interaction expected		Moderate severity CYP2C9 and CYP3A4inhibition: ↑acenocumarol levels	INR should be monitored within 1 week of onset	Moderate severity CYP3A4 inhibition: ↑acenocumarol levels	INR should be monitored within 1 week of onset
Dabigatran	No interaction expected	-	No interactions expected	-	Moderate severity P-gp inhibition: ↑dabigatran levels	Monitor for dabigatran toxicity. This combination should be avoided if CrCL <30 mL/min for atrial fibrillation or if CrCL <50 mL/min for other dabigatran indications	No interactions expected	-
Rivaroxaban	Minor severity CYP3A4 inhibition: ↑rivaroxaban levels	Monitor for rivaroxaban toxicity	Minor severity CYP3A4 inhibition: ↑rivaroxaban levels	Monitor for rivaroxaban toxicity	Major severity CYP3A4 inhibition: ↑ rivaroxaban levels	Avoid combination. Consider therapy modification	Minor severity CYP3A4 inhibition: ↑rivaroxaban levels	Monitor for rivaroxaban toxicity
Apixaban	Moderate severity CYP3A4 inhibition and P-glycoprotein mediated efflux of apixaban: ↑apixaban levels	Monitor for apixaban toxicity	Moderate severity CYP3A4 inhibition: ↑apixaban levels	Monitor for apixaban toxicity	Major severity CYP3A4 inhibition and P-glycoprotein mediated efflux of apixaban: ↑apixaban levels	Consider therapy modification. If necessary, adjust apixaban at 50% if receive 5 mg twice daily, and should not receive apixaban if receive 2.5 mg twice daily	Moderate severity CYP3A4 inhibition and P-glycoprotein mediated efflux of apixaban: ↑apixaban levels	Monitor for apixaban toxicity
Edoxaban	No interaction expected	-	No interaction expected	-	Moderate severity ↑ edoxaban levels	Consider therapy modification In patients treated for deep vein thrombosis or pulmonary embolism, reduce the edoxaban dose to 30 mg daily when combined with itraconazole. No dose adjustment is recommended for patients treated for atrial fibrillation.	No interaction expected	-
Systemic anticoagulants								
Enoxaparin	No interaction expected		No interaction expected		No interaction expected		No interaction expected	
Heparin	No interaction expected		No interaction expected		No interaction expected		No interaction expected	
Statins								
Atorvastatin	Moderate severity CYP3A4 inhibition: ↑atorvastatin	Monitor for atorvastatin toxicity and reduce atorvastatin dose when possible	Moderate severity CYP3A4 inhibition: ↑atorvastatin	Monitor for atorvastatin toxicity and reduce atorvastatin dose when possible	Moderate severity CYP3A4 inhibition and P-glycoprotein	Monitor for atorvastatin toxicity and reduce atorvastatin dose when possible	Moderate severity CYP3A4 inhibition ↑atorvastatin	Avoid combination

	levels		levels		mediated atorvastatin transport: ↑atorvastatin levels	maximum atorvastatin dose of 20 mg/day	levels	Switch to fluvastatin, rosuvastatin, pitavastatin, or pravastatin.
Simvastatin	Major severity CYP3A4 inhibition: ↑simvastatin levels	Avoid combination Switch to fluvastatin, rosuvastatin, pitavastatin, or pravastatin.	Moderate severity CYP3A4 inhibition: ↑simvastatin levels	Monitor for simvastatin toxicity Consider limiting simvastatin doses and using the lowest simvastatin dose necessary	Major severity CYP3A4 inhibition: ↑simvastatin levels	Avoid combination Switch to fluvastatin, rosuvastatin, pitavastatin, or pravastatin.	Major severity CYP3A4 inhibition: ↑simvastatin Levels	Avoid combination. Switch to fluvastatin, rosuvastatin, pitavastatin, or pravastatin.
Lovastatin	Major severity CYP3A4 inhibition: ↑lovastatin levels	Avoid combination Switch to fluvastatin, rosuvastatin, pitavastatin, or pravastatin	Moderate severity CYP3A4 inhibition ↑lovastatin levels	Monitor for lovastatin toxicity Maximum lovastatin dose of 20 mg/day	Major severity CYP3A4 inhibition: ↑lovastatin levels	Avoid combination Switch to fluvastatin, rosuvastatin, pitavastatin, or pravastatin.	Major severity CYP3A4 inhibition: ↑lovastatin levels	Avoid combination Switch to fluvastatin, rosuvastatin, pitavastatin, or pravastatin.
Pravastatin* **	No interactions expected	-	No interactions expected	-	Moderate severity CYP3A4 inhibition and P-glycoprotein mediated pravastatin efflux: ↑pravastatin Levels	Monitor for pravastatin toxicity	No interactions expected	-
Fluvastatin* **	↑ fluvastatin levels	Monitor for AE	No interactions expected	-	No interactions expected	-	No interactions expected	-
Pitavastatin* **	No interactions expected	-	No interactions expected	-	No interactions expected	-	No interactions expected	-
Rosuvastatin* **	No interactions expected	-	No interactions expected	-	Moderate severity ↑rosuvastatin levels	Monitor rosuvastatin toxicity and limit rosuvastatin dose to a maximum of 20 mg/day	No interactions expected	-
Gastroprotective drugs								
Omeprazole	Moderate severity CYP2C19, CYP2C9 and CYP3A4 inhibition: ↑voriconazole levels	Voriconazole TDM Consider reducing the omeprazole dose by 50% if using a daily omeprazole dose of 40 mg or higher	No interactions expected		Major severity pH-raising effect: ↓itraconazole levels	Use itraconazole solution Administer oral proton pump inhibitors at least 2 hours before or 2 hours after itraconazole	Major severity pH-raising effect: ↓ posaconazole levels	Use posaconazole delayed-release tablets
Pantoprazole	Moderate severity CYP2C19, CYP2C9 and CYP3A4 inhibition: ↑voriconazole levels	Voriconazole TDM	No interactions expected		Major severity pH-raising effect: ↓itraconazole levels	Consider therapy modification Administer oral proton pump inhibitors at least 2 hours before or 2 hours after itraconazole	Major severity pH-raising effect: ↓ posaconazole levels	Use posaconazole delayed-release tablets
Ranitidine	No interactions expected		No interactions expected		Major severity pH-raising effect: ↓itraconazole levels	Consider therapy modification to solution form Administer oral proton pump inhibitors at least 2 hours	Major severity pH-raising effect: ↓posaconazole levels	Use posaconazole delayed-release tablets

						before or 2 hours after itraconazole		
Famotidine	No interactions expected		No interactions expected		Major severity pH-raising effect: ↓itraconazole levels	Consider therapy modification	Major severity pH-raising effect: ↓posaconazole levels	Use posaconazole delayed-release tablets
Neuromuscular blockers								
Cisatracurium	No interactions expected		No interactions expected		No interactions expected		No interactions expected	
Rocuronium	No interactions expected		No interactions expected		No interactions expected		No interactions expected	
Sedative drugs								
Midazolam	Major severity CYP3A4 inhibition: ↑midazolam levels	Monitor for midazolam toxicity If necessary, ↓midazolam dose	Major severity CYP3A4 inhibition: ↑midazolam levels	Monitor for midazolam toxicity If necessary, ↓midazolam dose	Major severity CYP3A4 inhibition: ↑midazolam levels	Avoid combination Do not use oral midazolam with itraconazole or for 2 weeks after itraconazole discontinuation	Major severity CYP3A4 inhibition: ↑midazolam levels	Consider therapy modification
Propofol		Increased risk of QTc-prolonging effect Increased ECG monitoring may be considered in patients at high risk of QT interval prolongation	No interactions expected		No interactions expected		No interactions expected	
Dexmedetomidine	No interactions expected		No interactions expected		No interactions expected		No interactions expected	
Clonidine	No interactions expected		No interactions expected		No interactions expected		No interactions expected	
Ketamine	Moderate severity CYP3A4 inhibition: ↑ ketamine levels	Consider therapy modification If necessary, ↓ketamine dose	Moderate severity CYP3A4 inhibition: ↑ ketamine levels	Monitor for ketamine toxicity If necessary, ↓ketamine dose	Moderate severity CYP3A4 inhibition: ↑ ketamine levels	Consider therapy modification	Moderate severity CYP3A4 inhibition: ↑ ketamine levels	Consider therapy modification
Analgesics								
Morphine	No interactions expected		No interactions expected		Moderate severity P-glycoprotein/ABCB1 inhibition: ↑morphine levels	Monitor for morphine toxicity If necessary, ↓morphine dose	No interactions expected	
Fentanyl	Major severity CYP3A4 inhibition: ↑fentanyl	Consider therapy modification If necessary, ↓fentanyl dose	Major severity CYP3A4 inhibition: ↑fentanyl levels	Consider therapy modification If necessary, ↓fentanyl dose	Major severity CYP3A4 inhibition: ↑fentanyl levels	Consider therapy modification If necessary, ↓fentanyl dose	Major severity CYP3A4 inhibition: ↑fentanyl levels	Consider therapy modification If necessary, ↓fentanyl dose
Remifentanil	No interactions expected		No interactions expected		No interactions expected		No interactions expected	
Sufentanil	Major severity CYP3A4 inhibition: ↑sufentanil levels	Consider therapy modification If necessary, ↓sufentanil dose	Major severity CYP3A4 inhibition: ↑sufentanil levels	Monitor for sufentanil toxicity If necessary, ↓sufentanil dose	Major severity CYP3A4 inhibition: ↑sufentanil levels	Consider therapy modification If necessary, ↓sufentanil dose	Major severity CYP3A4 inhibition: ↑sufentanil levels	Consider therapy modification If necessary, ↓sufentanil dose
Vasoactive drugs								
Dobutamine	No interactions expected		No interactions expected		No interactions expected		No interactions expected	
Dopamine	No interactions expected		No interactions expected		No interactions expected		No interactions expected	

Norepinephrine	No interactions expected		No interactions expected		No interactions expected		No interactions expected	
Isoprenaline	No interactions expected		No interactions expected		No interactions expected		Moderate severity CYP3A4 inhibition: ↑ isoprenaline levels	Consider therapy modification If necessary, ↓isoprenaline dose
COVID-19 therapy								
Tocilizumab[71,72]£	No interactions expected	-	Moderate severity CYP3A4 induction: ↓isavuconazole levels	Isavuconazole TDM	Moderate severity CYP3A4 induction: ↓itraconazole levels	Itraconazole TDM	No interactions expected	-
Sarilumab[71,72]£	No interactions expected	-	Moderate severity CYP3A4 induction: ↓isavuconazole levels	Isavuconazole TDM	Moderate severity CYP3A4 induction: ↓itraconazole levels	Itraconazole TDM	No interactions expected	-
Baricitinib	No interactions expected	-	No interactions expected	-	No interactions expected	-	No interactions expected	-
Enoxaparin	No interactions expected	-	No interactions expected	-	No interactions expected	-	No interactions expected	-
Remdesivir		Monitor liver function ↑ risk of liver toxicity	No interactions expected	-	↑ risk of liver toxicity	Monitor liver function	↑ risk of liver toxicity	Monitor liver function
Hematology/Oncology								
Vinca alkaloids (vincristine)[73]	↑vincristine levels	Consider therapy modification	↑vincristine levels	Monitor for AE	↑vincristine levels	Consider therapy modification	↑vincristine levels	Consider therapy modification
Cyclophosphamide (High dose)[74,75]	-	-	-	-	↑cyclophosphamide levels	Monitor AE	-	-
Dasatinib[76]	↑dasatinib levels	Consider therapy modification	↑dasatinib levels	Consider therapy modification	↑dasatinib levels	Consider therapy modification If necessary, ↓ dasatinib dose#	↑dasatinib levels	Consider therapy modification
Venetoclax	↑venetoclax levels	Consider therapy modification∞	↑venetoclax levels	Monitor AE and limit venetoclax dose to 50%§	↑venetoclax levels	Consider therapy modification∞	↑venetoclax levels	Consider therapy modification¥
Midostaurin	↑midostaurin levels	Consider therapy modification	↑midostaurin levels	Monitor for AE	↑midostaurin levels	Consider therapy modification	↑midostaurin levels	↑midostaurin levels

INR: International normalized ratio; *ClCr:* Creatinine clearance.

Drug interactions information was consulted on: https://reference.medscape.com/drug-interactionchecker, https://www.drugs.com/drug_interactions.html, https://online.lexi.com/lco/action/interact and product's prescribing information documents. Specific references have been added based on the available literature.

*The small pharmacokinetic changes and conflicting results from various pharmacokinetic studies likely reflect the minor reliance of prednisolone on CYP3A4 for metabolic elimination and the strength of the CYP3A4 inhibitor. The magnitude of the interaction between strong CYP3A4 inhibitors and prednisone is markedly less than with methylprednisolone, a steroid that relies heavily on CYP3A4 for elimination.

** A study of 14 healthy volunteers reported no change in prednisolone pharmacokinetics with the coadministration of prednisone (60 mg single dose) after itraconazole treatment (400 mg on day 1, 200 mg daily on days 2 through 4)

***Fluvastatin, pitavastatin, pravastatin, and rosuvastatin may be safer alternatives since they are not metabolized by CYP450 3A4.

£Sarilumab and tocilizumab binds to and inhibits the proinflammatory cytokine interleukin-6 (IL-6).2 In vitro, IL-6 decreased CYP3A4 mRNA by greater than 90%. Sarilumab may restore CYP3A4 activity in RA patients and thus increase the metabolism of CYP3A4 substrates. This effect may persist several weeks following discontinuation of therapy due to the long half-life of sarilumab and tocilizumab.

Reduce dasatinib dose from 70 mg/day or 100 mg/day to 20 mg daily, or from 140 mg/day to 40 mg daily. For patients on dasatinib 40 mg or 60 mg daily, stop dasatinib until the CYP3A4 inhibitor is discontinued. Monitor patients closely for toxicity.

§ Resume the previous venetoclax dose 2 to 3 days after moderate CYP3A4 inhibitor discontinuation.

∞ Venetoclax prescribing information states that for patients being treated for CLL/SLL, use of strong CYP3A4 inhibitors is contraindicated during the initiation and ramp-up phase; after the ramp-up phase the steady daily dose of venetoclax should be reduced to 100 mg. Among patients being treated for AML, strong CYP3A4 inhibitors may be used during the initiation and ramp-up phase, but the venetoclax dose should be reduced to 10 mg on day 1, 20 mg on day 2, 50 mg on day 3, and 100 mg on day 4. The steady daily dose of venetoclax should be reduced to 100 mg in patients with AML receiving strong CYP3A4 inhibitors.

¥ Venetoclax prescribing information states that for patients being treated for CLL/SLL, use of posaconazole is contraindicated during the initiation and ramp-up phase; after the ramp-up phase the steady daily dose of venetoclax should be reduced to 70 mg if used concomitantly with posaconazole.1 Among patients being treated for AML, posaconazole may be used during the initiation and ramp-up phase, but the venetoclax dose should be reduced to 10 mg on day 1, 20 mg on day 2, 50 mg on day 3, and 70 mg on day 4.1 The steady daily dose of venetoclax should be reduced to 70 mg in patients with AML receiving concomitant posaconazole.